ABSTRACT

Despite proven efficacy of alemtuzumab in multiple sclerosis (MS), approximately 50% of individuals will develop a new autoimmune disease following treatment. To date these have largely been antibody mediated and organ specific (primarily affecting the thyroid gland). In a retrospective case series of 187 patients from two UK specialist centres (Cardiff and Cambridge) followed up for a median of 10 years, we report 3 (1.6%) cases of sarcoidosis following alemtuzumab treatment of MS. This report increases the spectrum of auto-inflammatory disease following alemtuzumab and should be considered by clinicians when using this therapeutic agent for MS.

INTRODUCTION

Alemtuzumab is an effective treatment for relapsing multiple sclerosis (MS), reducing relapse rates and partially reversing neurological disability.[1] However, approximately 50% of patients subsequently develop a secondary autoimmune disease (AID).[1] Thus far, this has largely been antibody mediated and organ specific, for example 40% of individuals develop thyroid autoimmunity (most commonly Graves' disease), 1-2% develop idiopathic thrombocytopenic purpura (ITP), and rare cases of Goodpasture's disease and other autoimmune cytopenias have been described.[2] Here we present three patients with MS, who developed systemic sarcoidosis following treatment with Alemtuzumab from two UK neuroscience centres.

CASE REPORTS

Case 1

A previously healthy 42-year-old female was diagnosed with MS following two relapses and confirmatory paraclinical investigations (Table 1). Following further relapses and active repeat MR imaging, alemtuzumab treatment was commenced. This was administered as a standard treatment regime (initial treatment cycle 12 mg/day intravenously for 5 consecutive days followed by 12 mg/day for 3 consecutive days 12 months later). The patient experienced a further relapse 3 years and 8 months following first dose and an annual MR brain scan revealed an increased T2 lesion load, having been previously stable. A third treatment cycle (12 mg/day for 3 days) was administered following which her disease has remained inactive.

Four years later she re-presented with a 6-month history of chest pain and shortness of breath. A chest X-ray (CXR) demonstrated bilateral hilar lymphadenopathy (Fig 1a). A computed tomography pulmonary angiogram (CTPA) revealed bilateral hilar, right supraclavicular fossa, right paratracheal, left superior mediastinal and right axillary lymphadenopathy (Fig 1b). Ground-glass shadowing was also present. These changes were not present on a CTPA performed 4 years earlier for investigation of pleuritic chest pain. Respiratory examination was normal with oxygen saturations of 97% on air.

Repeat CT, performed after a 3 month interval demonstrated additional cervical, para-aortic and retroperitoneal lymphadenopathy. Peri-bronchovascular nodularity was also seen suggestive of lung parenchymal involvement (Fig 1c). Cervical lymph node biopsy demonstrated non-caseating granulomas and changes considered consistent with sarcoidosis (Fig 1d). The patient subsequently developed breathlessness, which improved with oral corticosteroids. Repeat CT imaging has shown improvement. Of note, serum angiotensin converting enzyme (ACE) has remained within the normal range.

Case 2

A previously healthy 38-year-old female was diagnosed with MS following two relapses and supporting investigations (Table 1). Three further relapses occurred and she was commenced on subcutaneous interferon beta-1a. However, over the following 22 months, she experienced 4 more relapses and was switched to

natalizumab. She received 6 infusions but continued to experience frequent disabling relapses and was found to have neutralizing antibodies. Treatment was escalated to alemtuzumab, although 3 further relapses occurred during a planned washout period. Two courses of alemtuzumab were then administered according to the standard treatment regime 12 months apart with no further clinical relapses.

Three years and 9 months after alemtuzumab induction she presented with menorrhagia and was diagnosed with idiopathic thrombocytopenic purpura (ITP) - platelets 22 x 10^9/L. At that time, CXR (Fig 1e) revealed incidental right-sided hilar lymphadenopathy. CT subsequently demonstrated bilateral hilar, mediastinal, axillary and supraclavicular lymphadenopathy (Fig 1f). Lung function tests were normal. Sub-carinal lymph node core biopsy showed granulomatous inflammation (Fig 1g and h) in association with a raised serum ACE (66 units/L, local reference range 8-52 units/L), which had previously been normal. Respiratory medicine review confirmed a diagnosis of sarcoidosis but no therapeutic intervention was considered necessary.

Case 3

A 20-year-old otherwise healthy male presented with diplopia and unsteadiness. Three months later the patient developed right-sided face and arm sensory symptoms and a diagnosis of MS was made with supporting radiological and biochemical findings (Table 1). Alemtuzumab was commenced at the standard treatment regime, with further courses given following clinical relapses; 3, 10 and 12 years after initial treatment. Two years after the last treatment course, the patient

reported fatigue, reduced exercise tolerance, exertional dyspneoa and arthralgia. Later that year, he experienced bilateral eye pain with a marked distortion of the right pupil. Intermittent anterior uveitis was diagnosed and treatment commenced with cyclopentamine and dexamethasone eye drops with complete resolution of eye symptoms. Further investigation revealed a raised serum ACE of 123 iu/L (local reference range 20-82 iu/L) with mediastinal lymphadenopathy on CXR and CT (Fig 1i and j). A transbronchial needle aspiration of hilar lymph nodes revealed granulomata typical of sarcoidosis (Fig 1k and l). As his symptoms were relatively mild, he continues to be actively monitored without systemic immunosuppression.

Of note, all patients had a negative autoimmune screen at presentation and alternative diagnoses were excluded. All patients gave written consent for their case histories and images to be used in this manuscript.

DISCUSSION

Alemtuzumab, a humanised anti-CD52 monoclonal antibody, is an established treatment for active relapsing MS, with one phase II and two phase III trials confirming the marked effect on relapse frequency and slowing and/or reversing disability.[1] Its main effect is to cause rapid depletion of peripheral B- and T-lymphocytes with repopulation occurring through proliferation of mature lymphocytes that escape deletion (‘homeostatic proliferation’) and later by thymic repopulation with naïve cells derived from CD52-negative haematopoietic precursors.[1] This immune reconstitution is thought to be beneficial for disease outcomes.

Although having proven efficacy, secondary AID eventually occurs in approximately 50% of patients, with the thyroid gland the most common target.[3] Less commonly, patients may also develop ITP, haemolytic anaemia, autoimmune neutropaenia and glomerulonephritis.[2] To date the vast majority of autoimmunity seen after treatment has been antibody mediated and organ specific, although cases of vitiligo, alopecia and more recently haemophagocytic syndrome have been described.[4] Since alemtuzumab has only recently gained licensing approval, post-marketing surveillance remains essential to identify previously unrecognized adverse events and in particular those with potential autoimmune aetiology.

Sarcoidosis is a systemic disease characterized by granuloma formation predominantly affecting the lungs and lymphatic system.[5] The cause is unknown but an exaggerated cellular immune response to environmental stimuli such as mycobacteria and propionibacteria on a background of genetic susceptibility is considered likely. Through up-regulation of MHC class II molecules, alveolar macrophages are thought to act as antigen presenting cells with an influx of Th1 cells and absence of Tregs creating an unwanted inflammatory environment.[5] These activated T cells release IL-2 and other chemotactic factors for blood monocytes leading to further recruitment of macrophages and establishing a recurring inflammatory cycle that leads to granuloma formation.[6]

The development of sarcoidosis following alemtuzumab has only been reported once previously in the context of treatment for mycosis fungoides, an indolent T-cell

cutaneous lymphoma.[6] As suggested in that report,[6] we postulate that our patients are likely to have developed sarcoidosis as a result of homeostatic proliferation predisposing to autoimmunity. In further support of sarcoidosis resulting from immune reconstitution is the observation that sarcoidosis associated with human immunodeficiency virus (HIV) has increased in the era of highly active antiretroviral therapy (HAART).[7] Although neurosarcoidosis may have explained the initial presentation in these patients, we feel this is very unlikely and remain confident of the initial diagnosis of MS.

Although we have demonstrated a frequency of 1.6% for sarcoidosis in our cohort, this was not identified as a notable adverse event in either the phase II or phase III studies. The reasons for this remain unclear, however, the unique clinical characteristics of this cohort collated over 16 years, together with the length of follow-up may be relevant. Although there is a theoretical potential for sarcoidosis to have been unconnected to treatment with alemtuzumab, the plausible biology and frequency makes this unlikely. In addition to immune reconstitution, affected patients may also have been genetically susceptible and have been exposed to relevant environmental stimuli. Alemtuzumab has also recently been associated with monocytic/macrophage activation in the context of a patient with neuromyelitis optica;[8] following treatment, massive central nervous system infiltration of monocyte/macrophage infiltration was observed. As macrophages are a key component of sarcoidosis pathology, activation of these cells in certain at-risk patients may also contribute to disease pathogenesis.

Whilst the majority of observed autoimmune disease after alemtuzumab has been associated with the generation of antibodies, these cases highlight that other forms of autoimmunity can occur following treatment and should be considered as potential adverse events.

DISCLOSURES

J. Jones has received speaker honoraria from Sanofi Genzyme and has participated in scientific advisory boards for Sanofi Genzyme.

A. Coles has received honoraria for speaking at meetings, as well as travel and meeting expenses from Sanofi Genzyme

N. Robertson has received personal and institutional research grants from Sanofi Genzyme and Novartis.

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